PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application No.:	10/524,189	Group Art Unit:	1615
Filing Date:	September 15, 2005	Examiner:	Aradhana Sasan
Applicant:	Dirk Andre Richard VANDEN BERGHE		
Title:	METHOD FOR THE PREPARATION OF A SILICIC ACID COMPRISING EXTRUDATE, SAID EXTRUDATE, ITS USE AND A PHARMACEUTICAL COMPOSITION COMPRISING THE SAID EXTRUDATE		
Attorney Docket:	5100-000012/US		

DECLARATION PURSUANT TO 37 C.F.R. § 1.132

1. I, Chris Vervaet, a resident at the address Pieter Pruimstraat 11, 8870 Izegem, BELGIUM, declare as follows:

2. I received my Bachelor's and Master's degrees, and a PhD in Pharmaceutical Sciences from Ghent University, where I finished my education in 1997. My Ph.D. thesis related to the influence of process and formulation parameters on the quality of pellets produced by extrusion and spheronisation.

3. I am presently employed as a professor at Ghent University in the department of Pharmaceutics with special scientific interest in galenic formulations and pharmaceutical technology.

4. Because of my own education and experience evidenced above, I believe myself to be one of at least ordinary skill in the art of pharmaceutical sciences, specifically with regard to the field of making nutritional and pharmaceutical formulations by extrusion and spheronisation.

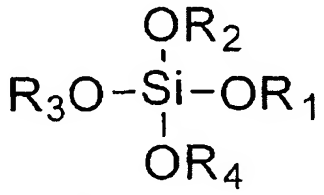
5. I have carefully read US Patent No. 5,922,360 (Bronder).

6. Bronder discloses the stabilization of orthosilicic acid (OSA) using as a nitrogen atom containing stabilizer choline. Choline is treated with dry hydrochloric acid and converted into choline hydrochloride. Choline is a solid and choline hydrochloride is a water free liquid. Subsequently, an inorganic silicon compound is added and hydrolyzed. OSA is formed in situ and stabilized by forming a complex with choline.

7. The presence of a nitrogen atom in choline is necessary to stabilize OSA, because the nitrogen atom comprises a free electron pair for forming a complex with the silanol group (see column 1, lines 59-62). The solution is partially neutralized by the addition of a base (see column 2, lines 18-39, and the preparation example). This OSA solution stabilized by choline may be used as a liquid formulation for oral or topical administration. The stabilized OSA solution may be mixed with cattle feed and pressed to pellets or tablets. Finally, the stabilized OSA solution may be used in a cream by mixing it with consecutively a fat phase, a water phase and a perfume (see the formulation examples A-D).

8. I have carefully read EP 1 110 909 (Vanden Berghe).

9. Vanden Berghe discloses the stabilization of orthosilicic acid (OSA) using a specific group of solvent agents. OSA is prepared by hydrolyzing an acid hydrolysable silicon compound having the following general formula, see [0005]:



wherein R_1, R_2, R_3 and R_4 are independently selected from H, C_1-C_{12} alkyl, C_1-C_{12} alkoxy which are optionally substituted by an hydroxyl group, under the proviso that R_1, R_2, R_3 and R_4 are not simultaneously H. Preferably, R_1, R_2, R_3 and R_4 are selected from H, C_1-C_4 alkyl, C_1-C_4 alkoxy optionally substituted by an hydroxylgroup. It is noted that R_1, R_2, R_3 and R_4 are preferably selected such that the compound split off from the hydrolisable silicon compound is removable using traditional techniques such as evaporation and distillation, and most preferably is non-toxic (LD_{50} orally in rat higher than 1g/kg bodyweight). The most preferred silicon compound is tetra-ethoxy-silanol.

10. OSA formed is stabilized by an alleged solvent agent. The group of solvent agents is defined as follows, see [0007]:

> [0007] The solvent agent used in the acid solution for stabilizing the formed ortho silicic acid may be selected from the group comprising glycol, glycerol, (poly)alkylene glycol, DMSO and polysorbate 80. The (poly) alkylene glycol may be polypropylene glycol or polyethylene glycol. The alkylene glycol may be ethylene glycol or propylene glycol. A common set of properties for all solvent agents are a high solubility in water (more than 30%), a boiling point higher than 130°C, a liquid state between -10°C and 40°C and a stability at an acid pH of generally 0-4.

11. The solvent agents are chemically characterized as compounds having two or more OH-groups, with the only exception of DMSO (dimethylsulphoxide) which is an dialkyl sulphoxide. These solvent agents are compounds without a nitrogen atom, such as (poly)ethylene glycol, (poly)propylene glycol, DMSO or polysorbate 80 which indicates that the stabilization mechanism of OSA by these solvent agents is not based on complexation via nitrogen atoms. The solvent agents are further defined by the following characterictics, see [0007]:

i. High water solubility (> 30%);

ii. Boiling point > 130°C;

iii. Liquid between -10°C and 40°C; and

iv. Stable at pH 0-4.

12. This OSA solution (stabilized by the solvent agent) may be further stabilized by the addition of a carrier of which examples are listed in [0015]. Microcrystalline cellulose is an example. After contact of the carrier with the OSA solution, the mixture may be extruded. Examples B and D give examples of extrusions. In example B, the solvent agent is glycerol and the carrier microcrystalline cellulose. The plastic mass formed is extruded and spheronized. In example D, the solvent agent was again glycerol and the carrier was a mixture of microcrystalline cellulose and fructans. This mixture was extruded and spheronized.

13. The preparation of example D was used in an in vivo experiment and compared with the liquid OSA solution of Bronder (see example F). It is reported and visualized in Fig. 2, that the total bioavailability of the carrier-bound OSA and of the liquid OSA is similar. Repeating the experiment one year after the production date of the carrier-bound OSA showed no differences in the results, which demonstrates a long term stability, see [0024].

14. I have carefully read the originally filed version of Application Serial No. U.S. Application No. 10/524,189 ("Application"), filed September 15, 2005.

15. The present invention claims a method for the preparation of a bioavailable silicic acid extrudate. It is reported that (a) the bioavailability of silicon largely depends on its chemical form ([0003]) and (b) it is very difficult to formulate a solid galenic preparation of silicic acid with a quaternary ammonium compound, such as choline, or an amino acid source due to gel formation and precipitation making the preparation non-bioavailable ([0004]). The alternative of direct filling of gelatine or methylcellulose capsules with a liquid matrix of choline stabilized silicic acid is not an option because such formulations result in leaking and deformation of the capsule. Dry choline is extremely hygroscopic and can attract water from the capsule which results in deformation of the capsule shell (page 1, second column, lines 2 – 7).

16. It is suggested to use the choline stabilized OSA solution in combination with a carrier which can be used in extrusion technology. The carriers are mentioned in page 3, second full paragraph. In the preparation example C and example D a 35% choline stabilized silicic acid solution was mixed with microcrystalline cellulose as carrier, and the wet mass was consecutively extruded, spheronized and dried until a water content below 5 % is obtained. In formulation example B such a preparation was tested in vivo. The results are shown in Figs. 2 and 3. It is reported that the bioavailability was comparable with the liquid solution according to Bronder. Furthermore, Table 3 shows that the extrudate has a positive effect on the bone mineral density (BMD) when compared with a placebo.

17. I understand that the in vivo experiments where OSA was stabilized by choline, both in the form of the liquid OSA formulation and in the form of the solid extrudate OSA formulation, have a comparable bioavailability, which was surprising to one at least of ordinary skill in the art.

18. It is my understanding that Vanden Berghe shows that OSA when stabilized with a specific group of solvent agents and applied on a carrier can be extruded; these solvent agents comprise compounds having 2 or more OH groups (and DMSO), are compounds without a nitrogen atom having a free

electron pair, are highly soluble in water, have a boiling point > 130°C, are liquid between -10 to 40C°, and are stable at pH 0-4; the stabilizer according to Bronder, choline, is not such a solvent agent or stabilizer. In Bronder, the stabilizer is choline hydrochloride solution formed by treating solid choline with dry hydrochloric acid. Choline hydrochloride does not include 2 or more OH groups (or resembles DMSO), have a boiling point below 130°C and contain a nitrogen atom for stabilization of OSA via complexation with a silanol group.

19. As choline is not chemically similar to these solvent agents, one of ordinary skill in the art would not have substituted a specific solvent agent by choline and expect that the obtained extrudate would have in vivo the same bioavailability as a Vanden Berghe extrudate and as a Bronder liquid choline stabilized formulation. Such substitution is not derivable from VandenBerghe, because VandenBerghe selected a chemically very different group of solvent agents or stabilizers, although Vanden Berghe had knowledge of the choline stabilization according to Bronder.

20. I would state that there is no suggestion or motivation in Bronder and in Vanden Berghe that choline would perform as a choline OSA complex in the same manner as the solvent agents OSA complex in an extrudate for providing the same bioavailability.

21. In addition, extrusion/spheronisation technology is a specific process which is different from the mixing of an orthosilicic acid solution with cattle feed and subsequent pressing in pellets or tablets as is described by Bronder.

22. It is for the reasons above that as one of at least ordinary skill in the art, I found it novel and unobvious that the substitution of a solvent agent according to Vanden Berghe by choline resulted in a stabilized OSA extrudate having the same bioavailability as a liquid choline stabilized OSA formulation and a solvent agent stabilized OSA formulation of Van den Berghe.

23. That it is declared by the undersigned that all statements made herein of undersigned's own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Title 18, U.S. Code 1001 and that such willful false statements may jeopardize the validity of this application or any patent issuing thereon.

Date: August 31st, 2009

Professor Chris Vervaet